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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,426	08/07/2000	Robert H. Zimmer	03187-P0006B	3123

7590 05/23/2005

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EXAMINER	
COTTON, ABIGAIL MANDA	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,426	ZIMMER, ROBERT H.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004 and 03 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6 and 17-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/3/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 1, 2004 has been entered. Claims 2-4, 6 and 17-24 are pending.

Applicant's arguments filed November 1, 2004, have been fully considered but they are not persuasive. In particular, the claim rejections made under 35 U.S.C 112, second paragraph, are being maintained, as are the claim rejections under 35 U.S.C. 103(a) over U.S. Patent No. 4,396,606 to Goldstein in view of U.S. Patent No. 4,694,006 to Bundgaard. New rejections of the claims are also being made.

Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract

on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The abstract of the disclosure is objected to because it contains more than one paragraph and contains the legal phraseology "comprises." Correction is required. See MPEP § 608.01(b).

Specification

The disclosure is objected to because of the following informalities: the word "formula" is repeated in tandem in the paragraph bridging pages 3 to 4, and in the second full paragraph on page 7. The word "drug" is misspelled in the first full paragraph on page 6. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-4, 6, 17-20 and 23-24 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-5, 8-12 and 17-20 of U.S. Patent Application Serial No. 10/050,903 (U.S. Patent Pub. No. 2002/0132777.) This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims claim a therapeutically active peptide species having the form aa_n, and a carrier moiety selected from a group of compounds that are the same in both the instant and published application. The claims differ in that the independent claims of the instant application specifically recite a "non-therapeutic linker species." However, as the non-therapeutic linker species may be an amino acid, as in instant claim 6, this limitation reads on the therapeutically active peptide species of formula aa_n as recited in claim 1 of U.S. Patent Application Serial No. 10/050,903. Accordingly, as the conflicting claims both recite a compound comprising the same elements, namely a therapeutically active peptide species and carrier moiety, the claimed prodrug of the instant application and the claimed pharmaceutical agent of U.S. Patent Application Serial No. 10/050,903 are obvious over one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite a therapeutic peptide that "is absorbed from about 0% to about 25% following its oral administration." The specification provides support for "only a 25% relative bioavailabilty of the active moiety (Enalaprilat)" and Lisinopril having "only a moderate oral bioavailability (<25%)" (Background of the invention), but does not provide support for a therapeutic peptide having a range of absorption of from about 0% to about 25%, as recited in the claims. Accordingly, the claims as presented are not supported by the disclosure of the originally filed application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 6, 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the term "substantially." The term "substantially" is a relative term that is not defined by the claims, and the specification also does not provide a standard for ascertaining the requisite degree. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-4, 6, 17-18 and 21-24 are rejected as depending upon indefinite base claims.

Claims 21 and 22 are furthermore rejected under 35 U.S.C. 112, second paragraph, for reciting the term "about," such as in "from about 0% to about 25%." The use of the term "about" in these claims is indefinite because it is not clear to one of ordinary skill in the art what range is being claimed. It is not clear what numeric ranges are included in such phrases as "about 0%" or "about 25%." The specification also does not provide any guidance as to what range is meant by "about" in these claims. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 21 and 22 are also rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "from about 0% to about 25%," because it is not clear what unit the percentage is referring to. It is not clear if the recited percentages are intended to be a percent by weight of the therapeutic peptide, a percent by mole, or some other unit. The specification also does not provide any guidance as to the intended units. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 21-24 are rejected under 35 U.S.C. 112, second paragraph, due to a lack of proper antecedent basis for the term "said therapeutic peptide." Claims 19 and 20, from which claims 21-24 depend, recite a "therapeutic polypeptide," but do not recite a "therapeutic peptide," and thus antecedent basis for this term is not present in these base claims. Appropriate correction is required.

Claims 2-4, 6 and 17-24 are also rejected under 35 U.S.C. 112, second paragraph, for reciting the phrase "therapeutic polypeptide is one," as in claims 19-20, and the phrase "therapeutic peptide is one" as in claims 21-24, because it is not clear what "one" peptide is being referred to. The specification furthermore does not provide any guidance as to what is meant by the "one" peptide or polypeptide. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-4, 6 and 17-18 are rejected as being dependent upon indefinite base claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-3, 6, 19-20 and 23-24, are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,624,894 to Bodor, issued April 29, 1997.

Bodor discloses novel peptide derivatives designed to deliver pharmacologically active peptides into the central nervous system (see abstract, in particular.) The pharmacologically active peptide (from 2 to 20 amino acids long), is linked to a dihydropyridine-type redox moiety via an amino acid spacer peptide (see abstract and column 15, lines 1-44, in particular.) Bodor further teaches providing a "hydroxyl protective group" that is inserted in place of a hydrogen atom of an OH group to protect the OH group during synthesis and/or to improve lipoidal characteristics and prevent premature metabolism of the OH groups (see column 18, lines 15-40, in particular.) Bodor teaches that such protective groups are frequently used during synthesis of the "spacer-peptide" section of the molecule and can be retained in the final product (see column 18, lines 15-40 in particular.) Bodor teaches that suitable hydroxyl protective

groups include benzoyl and phenylacetyl groups (see column 19, lines 20-50, in particular.) Accordingly, Bodor teaches providing a pharmacologically active polypeptide that is linked to an amino acid spacer, the amino acid spacer having a hydroxyl protective group that is, for example, a benzoyl or phenacetayl carrier moiety, as in the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3-4, 6, 17-20 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,396,606 to Goldstein, issued August 2, 1983, in view of U.S. Patent No. 4,694,006 to Bundgaard et al, issued September 15, 1987.

Goldstein teaches opioid compounds having phenolic hydroxyl linked to a polypeptide with at least one amino acid (see abstract and column 1, line 65 through column 2, line 6, in particular.) Goldstein teaches met-enkephalin and leu-enkephalin are taught as polypeptide opioids (see column 1, lines 5-23, and column 4 line 63-66, in particular.) Goldstein also teaches that two amino acids (non-therapeutic linker

species) can be provided at the n-terminus of the oligopeptide (see column 3, lines 39-55, in particular.) Goldstein further teaches that there has been substantial activity in trying to develop modifications of leu-and met-enkephalin to enhance their activity, including modifications to the ends of the polypeptide chains (see column 1, lines 5-37, in particular.)

It should be further noted that a single amino acid species, such as an amino acid from the enkephalin polypeptide taught by Goldstein, is considered to constitute a "non-therapeutic linker species," as recited in the instant claims, as a single amino acid on its own is not expected to have a therapeutic effect.

Goldstein does not teach the specific carrier moiety of the instant claims.

Bundgard et al. teaches a prodrug form of allopurinol that provides improved aqueous solubility/and or higher lipophilicity, and improved oral administration as compared to the parent compound (see abstract and column 1, line 6 through column 2, line 47, in particular.) Bundgaard et al. teaches providing the improved prodrug forms by attaching an acyl group such as benzoyl or cinnamoyl (see column 5, lines 65 through column 7, line 53, and column 10, lines 60 through column 11, lines 23, in particular.)

Accordingly, it would have been obvious to one of ordinary skill in that art at the time the invention was made to have modified the opioid polypeptide of Goldstein by linking an acyl group such as cinnamoyl or benzoyl as taught by Bundgaard et al, because Goldstein teaches the desirability of modifying the opioid polypeptide to enhance activity, and Bundgaard et al. teaches that such acyl groups provide prodrugs having improved solubility and oral administration. Thus, one of ordinary skill in the art would have been motivated to link the acyl group of Bundgaard et al. to the met-enkephalin or other opioid of Goldstein with the expectation of achieving a prodrug with the improved solubility and oral administration.

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldstein and Bundgaard et al. as applied to claims 2, 3-4, 6, 17-20 and 23-24 above, and further in view of the Background section of Applicant's own specification.

Goldstein and Bundgaard et al. are applied as discussed above. Goldstein and Bundgaard et al. do not specifically teach that a therapeutic peptide is absorbed from 0% to about 25% following its oral administration.

Applicant teaches in the Background section of the instant application that therapeutically effective oligopeptides with two or more amino acids are poorly absorbed orally, and further teaches as an example that Lisinopril, having two amino

acids, is known to have only a moderate oral bioavailability of less than 25% (see Background of the Invention, first full paragraph, in particular.)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Goldstein, Bundgaard et al. and Applicant's own admitted prior art teachings to provide the claimed prodrug having a therapeutic polypeptide that is absorbed in an amount of from about 0% to about 25%, because Goldstein teaches the desirability of modifying a polypeptide to enhance activity, Bundgaard et al. teaches the use of acyl groups to provide prodrugs having improved solubility and oral administration, and Applicant's own admitted prior art teaches an example of a polypeptide that is absorbed in the claimed amount of from about 0% to about 25%. Thus, one of ordinary skill in the art would have been motivated to link the acyl group of Bundgaard et al. to the poorly absorbed polypeptide taught in Applicant's own admitted prior art with the expectation of enhancing the activity of the polypeptide, such as the solubility and oral administration of the polypeptide, as taught by the combined polypeptide enhancement teachings of Goldstein and Bungaard et al.

Claims 2, 3-4, 6, 17-20 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract "Prodrugs of Peptides 15. 4 Imidazolidinone Prodrug Derivatives of Enkephalins to Prevent Aminopeptidase-Catalyzed Metabolism in Plasma

and Absorptive Mucosae" by Rasmussen et al. (BIOSIS No. 199293044542, 1991), in view of U.S. Patent No. 4,694,006 to Bundgaard et al, issued September 15, 1987.

Rasmussen et al. discloses providing prodrugs of enkephalins by condensing with aldehydes or ketones to form 4-imidazolidinone derivatives (see abstract, in particular.) Ramussen et al. teaches that the prodrugs were almost totally resistant to enzymatic cleavage and were readily converted to the parent peptides by spontaneous hydrolysis (see abstract, in particular.) Rasmussen et al. furthermore teaches that the 4-imidazolidinone formation may be a useful approach to protect the N-terminal amino acid residue of enkephalins against cleavage by aminopeptidases and to obtain transport forms with improved lipophilicity (see abstract, in particular.)

It should be noted that a single amino acid species, such as an amino aid from the enkephalins taught by Rasmussen et al, is considered as constituting a "therapeutic linker species" as recited in the claims, as a single amino acid on its own is not expected to have a therapeutic effect.

Rasmussen et al. does not teach the specific carrier moieties recited in the claims.

Bundgaard et al. teaches a prodrug form of allopurinol that provides improved aqueous solubility/and or higher lipophilicity, and improved oral administration as

compared to the parent compound (see abstract and column 1, line 6 through column 2, line 47, in particular), as discussed above. Bundgaard et al. teaches providing the improved prodrug forms by attaching an acyl group such as benzoyl or cinnamoyl (see column 5, lines 65 through column 7, line 53, and column 10, lines 60 through column 11, lines 23, in particular.)

Accordingly, it would have been obvious to one of ordinary skill in that art at the time the invention was made to have modified the enkephalin prodrugs of Rasmussen et al. by linking an acyl group such as cinnamoyl or benzoyl as taught by Bundgaard et al, because Rasmussen et al. teaches the desirability of forming prodrugs of enkaphalins to provide improved properties, and Bundgaard et al. teaches that such acyl groups provide prodrugs having improved solubility and oral administration. Thus, one of ordinary skill in the art would have been motivated to link the acyl group of Bundgaard et al. to the enkephalins of Rasmussen with the expectation of achieving a prodrug with the improved solubility and oral administration.

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. and Bundgaard et al. as applied to claims 2, 3-4, 6, 17-20 and 23-24 above, and further in view of the Background section of Applicant's own specification.

Rasmussen et al. and Bundgaard et al. are applied as discussed above. Rasmussen et al. and Bundgaard et al. do not specifically teach that a therapeutic peptide is absorbed from 0% to about 25% following its oral administration.

Applicant teaches in the Background section of the instant application that therapeutically effective oligopeptides with two or more amino acids are poorly absorbed orally, and further teaches as an example that Lisinopril, having two amino acids, is known to have only a moderate oral bioavailability of less than 25% (see Background of the Invention, first full paragraph, in particular.)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Rasmussen et al, Bundgaard et al, and Applicants own admitted prior art teachings to provide the claimed prodrug having a therapeutic polypeptide that is absorbed in an amount of from about 0% to about 25%, because Rasmussen et al. teaches the desirability of forming prodrugs of enkaphalin polypeptides to provide improved properties, Bundgaard et al. teaches the use of acyl groups to provide prodrugs having improved solubility and oral administration, and Applicant's own admitted prior art teaches an example of a polypeptide that is absorbed in the claimed amount of from about 0% to about 25%. Thus, one of ordinary skill in the art would have been motivated to link the acyl group of Bundgaard et al. to the poorly absorbed polypeptide taught in Applicant's own admitted prior art with the expectation of enhancing the activity of the polypeptide, such as the

solubility and oral administration of the polypeptide, as taught by the combined polypeptide enhancement teachings of Rasmussen et al. and Bungaard et al.

Response to Arguments

Applicant's arguments filed November 1, 2004 have been fully considered but they are not persuasive.

Applicant argues that the term "substantial" is not an indefinite term. 35 U.S.C. 112, second paragraph, requires that the claims be written such that they point out and distinctly claiming the subject matter which the applicant regards as his invention. The present claims recite, for example, "wherein the therapeutic polypeptide is one substantially not absorbed following its oral administration." Thus, the term "substantially" as used in the claims is not clear to one of ordinary skill in the art, as it is not clear what amount or range is intended by "substantially not absorbed." To what extent or degree must something not be absorbed in order to be "substantially not absorbed?" Accordingly, one of ordinary skill would not be apprised of the scope of the invention because it is not clear what therapeutic polypeptides are those that are substantially not absorbed.

Applicant furthermore argues that the specification provides adequate support for the phrase "substantially not absorbed." In the Background section to which the

Applicant refers, the pro-drug Enalapril is disclosed as having only a 25% relative bioavailability of the active moiety, and Lisinopril is disclosed as having "moderate" oral bioavailability of less than 25%. Thus, the specification discloses a percentage bioavailibility for two prodrug examples. However, the specification does not define what absorption value is intended by the term "substantially not absorbed," and does not even define a relationship between a percent bioavailability and an amount absorbed such that the claimed phrase would be clear based on a given bioavailability. The specification does not state that the bioavailability is equal to the percent absorbed, and in contrast appears to indicate that the bioavailability is a function of the amount absorbed as well as the amount that is released from in vivo cleavage of the prodrug. The specification also does not define "substantially not absorbed" or even "percent bioavailability" for general therapeutic polypeptides other than Enalapril and Lisinopril, and thus does not apprise one of ordinary skill in the art as to the solubility extent that would render other polypeptides suitable. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the claim because it is not clear what therapeutic polypeptides are encompassed by the phrase "substantially not absorbed."

Applicant furthermore argues that there is no suggestion or motivation in the prior art to combine the teachings of the Goldstein and Bundgaard et al. references. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is

some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Goldstein teaches modifying prodrug compounds such as opioid compounds to provide improved activity, as described above. Bundgaard et al. discloses improving the solubility and oral administration of prodrugs by chemically linking to an acyl moiety such as benzoyl or cinnamoyl. Accordingly, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the opioid compound of Goldstein with the acyl group of Bundgaard et al. with the expectation of achieving a prodrug with improved solubility and oral administration.

Applicant argues that Goldstein does not teach a combination of an amino terminal-linked carrier and non-therapeutic linker. As noted above, Goldstein teaches a spacer between an oligopeptide and an opioid compound that comprises at least two amino acids. Furthermore, as a single amino acid is not expected to have therapeutic activity on its own, a single amino acid from the enkephalin derivative of Goldstein is interpreted as constituting a non-therapeutic linker. Regarding the amino terminal-liked carrier, it should be noted that claims 2-4, 6 and 18-24 do not require the feature that Applicant is relying on, namely that the carrier be amino terminal-linked. Although the claims are interpreted in light of the specification, limitations from the specification are

not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding Applicant's argument that Bundgaard et al. does not teach the use of a carrier for increased bioavailability of a peptide, the Examiner notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding Applicant's argument that the Goldstein patent doesn't mention or purport to address the well-known problem of poor gastro-intestinal absorption peptide therapeutics. As admitted by Applicants, poor gastro-intestinal absorption of peptide therapeutic is well-known, and poor bioavailability of peptides is also described in the Background section of Applicant's specification. Goldstein teaches that polypeptide therapeutics can be beneficially modified, and Bundgaard teaches improving oral administration with carrier moieties. Accordingly, one of ordinary skill in the art at the time the invention was made would find it obvious to modify the therapeutic peptides of Goldstein according to Bundgaard et al.

Regarding Applicant's argument that Goldstein teaches away from the current invention by teaching that a phenolic group is likely to mediate opioid receptor binding: Goldstein is being relied on to teach the desirability of modifying an opioid compound.

In the section to which the Applicant refers, Goldstein teaches that met-enkephalin has a tyrosine group that is analogous to the phenolic group of morphine. A teaching of providing an analogous compound such as met-enkephalin does not constitute a teaching against modifying a polypeptide therapeutic to provide enhanced activity.

Regarding Applicant's claim that Bundgaard et al. does not teach or suggest that a carrier moiety such as cinnamoyl or benzoyl would be useful in increasing the bioavailaility of a peptide drug: Bundgaard et al. discloses modifying a prodrug by chemically linking to moieties to increase the solubility and improve oral administration. Cinnamoyl and benzoyl are taught as moieties suitable for forming the improved pro-drug.

Regarding Applicant's argument that Bundgaard et al. doesn't address poorly absorbed small molecule drugs: Bundgaard et al. teaches improving the solubility and oral administration of prodrugs, as discussed above.

Regarding Applicant's argument that "benzoyl" and "cinnamoyl" appear in a "laundry list" disclosure of possible moieties by Bundgaard et al: Bundgaard et al. lists moieties that are suitable for use in improving the solubility and oral administration of a prodrug. One of ordinary skill in the art would thus find it obvious to provide such a moiety when seeking to modify a prodrug to provide improved solubility and oral administration.

Regarding Applicant's argument that the prior art does not provide a reasonable expectation of success: Goldstein teaches that prodrugs comprising therapeutic peptide compounds can be modified to improve activity, including at the ends of the peptide chains. Bundgaard et al. teaches that prodrugs can be modified with the recited carrier moiety. Accordingly, one of ordinary skill in the art would have a reasonable expectation that an end of the therapeutic polypeptide chain of Goldstein could be modified by the carrier moiety of Bundgaard et al.

Applicant further argues that the Examiner is misconstruing the term "prodrug" to include compounds that are not limited to the prodrug as defined in the specification. A prodrug is generally defined as a chemical compound that is converted into an active curative agent by metabolic processes within the body. Thus, by definition a prodrug is not limited to those compounds that have a therapeutic peptide, a linker, and a carrier moiety as defined by Applicant, but also generally includes other compounds that are converted into active curative agents by metabolic processes, such as the allopurinal prodrugs of Bundgaard et al. While Applicant is entitled to be his own lexicographer, it is also true that, for the purposes of examination, the claims are given their broadest reasonable interpretation in light of the supporting disclosure. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).

Regarding Applicant's argument that the prodrug of Bundgaard et al. is different from the peptide therapeutic recited in the claims: the Examiner does not dispute the fact that the allopurinol prodrug of Bundgaard et al. is not an amino acid polypeptide. However, Bundgaard et al. does teach chemical moieties that are of use in improving the activities such as the solubility and oral administration of prodrugs, and thus in combination with the teachings of Goldstein renders the claims obvious.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant furthermore argues that problems of oral administration of peptide therapeutics pose disparate challenges over small molecule drugs. Evidence of such disparate challenges may be presented in a timely filed declaration under 35 U.S.C. 132 for consideration by the Examiner. However, it is noted that Goldstein nevertheless teaches the desirability of modifying polypeptide compounds to improve activity.

Regarding Applicant's argument that the cited references do not teach or suggest each and every element of the claim, and specifically do not teach the use of an amino terminal peptide linking the carrier molecule to the therapeutic peptide: Goldstein teaches an amino acid linker, as discussed above. Furthermore, the limitation that the linker is an amino terminal peptide is not recited in rejected claims 2-4, 6 and 18-24. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 8:30-5:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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AMC

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